UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/672,784	09/26/2003	Page W. Caufield	1049-1-035N	9694

23565 7590 05/09/2006

KLAUBER & JACKSON
411 HACKENSACK AVENUE
HACKENSACK, NJ 07601

EXAMINER	
HINES, JANA A	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 05/09/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/672,784	CAUFIELD ET AL.	
	Examiner	Art Unit	
	Ja-Na Hines	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/11/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claim Status

1. Claims 1-21 are under consideration in this office action.

Information Disclosure Statement

2. The information disclosure statement (IDS) submitted on August 11, 2005 was entered. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 17-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a) Claim 17 recites the limitation "the initial pH" in the claim. There is insufficient antecedent basis for this limitation in the claim.

b) Claim 20 recites the limitation "the fermentation broth" in the claim. There is insufficient antecedent basis for this limitation in the claim.

c) Claim 21 recites the limitations "the emulsion layer" and "the chloroform and aqueous phases" in the claim. There is insufficient antecedent basis for these limitations in the claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 1-3, 5-7, 9-10, 12-14, 17-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Novak et al., in view of Delisle. The claims are drawn to a method of producing a mutacin comprising (a) growing a mutacin producing cell in a liquid medium under conditions in which mutacin is produced, wherein the liquid medium comprises yeast extract, peptone, sucrose and salts; and (b) isolating mutacin from the liquid medium. The dependant claims are drawn to specific ranges for the medium components, specific types of mutacins and cells, and additional mutacin isolation steps.

Novak et al., teach the isolation of a novel lantibiotic mutacin from *Streptococcus mutans*. Several species of bacteria including *S. mutans* produce antimicrobial substances referred to as bacteriocins (page 4316). Mutacins are a type of bacteriocin also produced by *S. mutans* (page 4316). For purposes of isolating mutacin from liquid culture, the *S. mutans* producer was grown in a chemically defined medium (CDM) (page 4316). Components of the CDM medium include 0.2g of K_2HPO_4, and 0.7g of $MgSO_4 \bullet 7H_20$. The final pH of the CDM was between 6.95 and 7.05. Novak et al., references van de Rijn et al., as teaching the makeup of the CDM liquid medium. This medium is supplemented with commercially available yeast extract at 3% and

Trypticase Soy Broth (TSB) (page 4316). The TSB was purchased from Difco Laboratories. TSB has a well known chemical makeup as evidenced by the enclosures from BD Diagnostic Systems which now owns Difco, Sigma-Aldrich Catalogue and the U.S. Food and Drug Administration Bacteriological Analytical Manual. TSB commonly contains 17g trypticase peptone, also known as casein peptone; 3g Phytone peptone, also known as soya peptone; 5g sodium chloride; 2.5g dipotassium hydrogen phosphate (K_2HPO_4); and 2.5g glucose. Thus the art teaches a liquid medium comprising yeast extract, peptones, glucose as the carbon source and salts within the instantly claimed ranges. For mutacin purification, the cell culture was anaerobically incubated in a 2 liter flask (page 4317). An equal volume of chloroform was added (page 4317). The emulsion formed between the aqueous and chloroform layers was dried, washed, solubilized and precipitated by centrifugation (page 4317). Thus the art teaches that mutacin was isolated from the liquid culture, extracted with chloroform and the emulsion layer formed between the chloroform and aqueous phases centrifuged to isolated the mutacin just as required by the claims. However, Novak et al., do not recite the use of sucrose as a carbon source in the liquid medium.

Delisle teach the production of bacteriocins in a liquid medium by *Streptococcus mutans*. The media including yeast extracts were obtained from BBL (page 707). The broth media included trypticase soy broth (TSB), APT broth and other nutrient broth (page 707). All the media was purchased from BBL Laboratories. TSB and APT have a well known chemical makeup as evidenced by the enclosure from BD Diagnostic Systems which now owns Difco and BBL. The APT broth comprises reagents including

12.5g casein peptone, 7.5g yeast extract, 5.0g sodium chloride (NaCl), and 0.8g magnesium sulfate ($MgSO_4$). The liquid medium finally developed for bacteriocin production contained 4% yeast extract (page 707). It was found that high concentrations of yeast extract did in fact allow for more bacteriocin synthesis in broth cultures, when the media contained 3 to 6% yeast extract (page 708). The cell culture was neutralized to pH 7.0 (page 708). The authors tested different carbon sources, such as 5 to 50g of glucose, sucrose, fructose, and galactose and pH's ranging from 5.5 to 8.0 (page 709). Thus the art teaches a liquid medium comprising the instantly recited carbon source within the instantly claimed ranges. The optimum temperature and pH conditions for bacteriocin production were found to be 37 °C and pH's of 6.0 to 7.4, respectively (page 709). Thus the art teaches a liquid medium having temperatures and pH's within the instantly claimed ranges. For the extraction of the bacteriocin, the liquid medium grown cells were collected and centrifuged (page 708). The pellets were resuspended in various solvents and salts including chloroform (page 708). Thus the art teaches isolation from the liquid culture, using chloroform and centrifugation just as required by the claims.

Therefore, it would have been prima facie obvious at the time of applicants' invention to modify the method of production to exchange the glucose carbon source as taught by Novak et al., for the sucrose carbon source as taught by Delisle. No more than routine skill would have been required to exchange sucrose for glucose when the art teaches the use of alternative yet functionally equivalent carbon sources such as sucrose, glucose and fructose within the method of producing mutacin bacteriocins.

Furthermore, one of ordinary skill in the art would have a reasonable expectation of success since the art teaches a method of production using the many of the same reagents, at similar levels within the same method steps to achieve similar results since no more than routine skill is involved in adjusting the amount of a component of the claimed process to suit a particular starting material in order to achieve the results taught in the prior art.

5. Claims 1-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Qi et al., in view of DeVuyst et al. The claims are drawn to a method of producing a mutacin comprising (a) growing a mutacin producing cell in a liquid medium under conditions in which mutacin is produced, wherein the liquid medium comprises yeast extract, peptone, sucrose and salts; and (b) isolating mutacin from the liquid medium. The dependant claims are drawn to specific ranges for the medium components, specific types of mutacins and cells, and additional mutacin isolation steps.

Qi et al., teach the ability of *Streptococcus mutans* to produce mutacins combined with its lactic acid production (page 388). Qi et al., further teach the purification of mutacin III from group III *S. mutans* UA787. The Materials and Methods section teach the use of the *S. mutans* UA787 (page 3881). For propagation the bacteria were grown on Trypticase Soy Broth plus Yeast extract (TSBY) containing 3% of TSB which has a final pH of 7.3+/-0.2 and yeast extract (page 3881). Thus the art teaches a liquid medium having pH's within the instantly claimed ranges. The Trypticase Soy Broth plus Yeast extract (TSBY) contains 17g trypticase peptone, also known as

casein peptone; 3g Phytone peptone, also known as soya peptone; 5g sodium chloride; 2.5g dipotassium hydrogen phosphate (K_2HPO_4); and 2.5g glucose plus yeast extract. For the isolation and purification of mutacin III, the plates were supplemented with 1g of K_2HPO_4; 0.7g of $MgSO_4 \cdot 7H_20$ (page 3881). Thus the art teaches a liquid medium comprising yeast extract, peptone, and salts, just as recited by the claims. The culture was transferred in a centrifuge and then extracted with an equal volume of chloroform (page 3881). The emulsion at the chloroform-aqueous interface was collected by centrifugation (page 3881). Therefore, the art teaches that mutacin was isolated from the liquid culture, extracted with chloroform and the emulsion layer formed between the chloroform and aqueous phases centrifuged to isolated the mutacin just as required by the claims. Qi et al., also each that mutacin III is a lantibiotic peptide which shares structural features with the lantibiotics in the nisin group (page 3882). However, Qi et al., do not recite the use of sucrose in the liquid medium.

DeVuyst et al., teach lactic acid bacteria produce a wide variety of peptide antibiotics, bacteriocins and lantibiotics (page 571). DeVuyst et al., studied the influence of the carbon source on the production of the lantibiotic nisin. The bacteria cell culture medium contained 10g of sucrose, 10g of peptone, 10g of yeast extract, 10g of KH_2PO_4, 2.0g of NaCl, 0.2g of $MgSO_4 \cdot 7H_20$ (page 572). Thus the art teaches a liquid medium comprising yeast extract, peptone, and salts, just as recited by the claims. The initial pH was adjusted to 6.8 (page 572). Thus the art teaches a liquid medium having an initial and final pH within the instantly claimed ranges. DeVuyst et al., teach using sucrose amounts from 10g to 100g (page 573). Therefore, the art teaches using sucrose within

the instantly claimed ranges. Table 1 teaches the influence of initial sucrose concentration on the bacterium. The authors noted that increasing the sucrose levels to 20g increased biomass levels 1.5 times (page 576). The authors also noted that with sucrose concentrations higher than 40g, both biomass and nisin titres decreased (page 576). Thus the authors teach the use of sucrose in a liquid medium for growing lantibiotic producing cells. DeVuyst et al., teach that fermentation was run in Erlenmeyer flask and in a fermenter (page 572). Thus, the authors teach the methods running under fermentation conditions, just as required by the claims. The flasks were incubated at without agitation while the fermenter was operated without aeration wherein slow agitation (50 rpm) was continuously provided to keep the fermentation broth homogenous (page 572). Thus the art teaches fermentation conducted within the instantly claimed agitation rates.

Therefore it would have been prima facie obvious at the time of applicants' invention to modify the method of production to exchange the glucose carbon source as taught by Qi et al., for the sucrose carbon source as taught by DeVuyst et al. No more than routine skill would have been required to exchange sucrose for glucose when the art teaches the use of alternative yet functionally equivalent carbon sources such as sucrose, glucose and fructose within the method of producing lantibiotic bacteriocins. Furthermore one of ordinary skill in the art would have a reasonable expectation of success since the art teaches a method of producing similar lantibiotic bacteriocins using the many of the same reagents, at similar levels within the same method steps to achieve similar results. No more than routine skill is involved in exchanging the sucrose

component within a similar the process of production as taught by DeVuyst et al., in order to achieve the results taught in the prior art since DeVuyst teaches optimizing conditions, reagents and steps using a related lantibiotic bacteriocin in another lactic acid producing bacteria.

Prior Art

6. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. US Patent 5,837,485 teach the production of a lantibiotic wherein the bacteria was cultured in a liquid medium comprising peptone, yeast extract, glucose, NaCl, K_2HPO_4 at a 7.5 pH. Hamada et al., teach effective growth of *S. mutans* in sucrose containing culture media. Hickmann et al., teach nisin production in a fermentor using whey permeate supplemented with sucrose, peptone, yeast extract, and salts KH_2PO_4, NaCl and $MgSO_4$ in a liquid medium. Qi et al., (1999. Applied and Environ. Microbio. Vol. 65(2): 652-658) teach mutacin II produced by *S. mutans* grown anaerobically at 37°C in commercially available CDM-TSBY liquid medium. Qi et al., also teach mutacin isolation, using a centrifuge followed by extraction with chloroform to allow the collection of the proteinous interface.

Conclusion

7. No claims allowed.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ja-Na Hines whose telephone number is 571-272-0859. The examiner can normally be reached on Monday-Thursday and alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on 571-272-0864. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Ja-Na Hines
April 18, 2006

L. F. Smith
LYNETTE R. F. SMITH
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600